Remarks

Claims 17, 20-26 and 30-32 are pending in the subject application. By this Amendment, Applicants have canceled claims 30 and 36-42, amended claims 17, 20 and 21. Support for the amendments can be found throughout the subject specification and in the claims as originally filed. Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 17, 20-26 and 31-35 are currently before the Examiner with claims 21 and 23 standing withdrawn from consideration. Favorable consideration of the pending claims is respectfully requested.

Applicants gratefully acknowledge the Examiner's withdrawal of the objections to the specification and the rejections under 35 U.S.C. § 112, second paragraph, and 35 U.S.C. § 102(b) and § 103(a).

Claims 17, 20, 22, 24-26 and 30-42 are rejected under 35 U.S.C. § 112, first paragraph, as nonenabled by the subject specification. The Office Action indicates that the specification is enabled for a method of producing the recombinant TBP-1 of SEQ ID NO:1 in a CHO cell but is not enabled for a method of producing a mutein which is less than 100% identical to SEQ ID NO: 1 or encoded by polynucleotides which hybridize to polynucleotides encoding SEQ ID NO: 1, as well as for using all cells other than CHO cells. Applicants respectfully assert that the claims as filed are enabled; however, the claims have been amended to indicate that the mammalian cell line is a CHO cell line that comprises a DNA sequence encoding a TBP-1 polypeptide comprising SEQ ID NO: 1 in order to expedite prosecution of this matter. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph, is respectfully requested.

Claims 17, 20, 22, 24-26 and 30-42 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The Office Action states that the specification and claims do not indicate what distinguishing attributes are shared by the members of the genus. Applicants respectfully assert that there is adequate written description in the subject specification to convey to the ordinarily skilled artisan that they had possession of the claimed invention; however, the claims have been amended in a fashion that renders this issue moot and expedite prosecution of this matter.

Accordingly, reconsideration and withdrawal of the rejections under 35 U.S.C. § 112, first paragraph, is respectfully requested.

Claim 20 is rejected under 35 U.S.C. § 112, second paragraph, as indefinite in the recitation of "moderate" and "stringent conditions". Applicants respectfully assert that the claims as filed are definite. However, the amendments made to claim 20 have rendered this issue moot and reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, second paragraph, is respectfully requested.

Claims 17, 20, 22, 24-26 and 30-42 are rejected under 35 U.S.C. § 103(a) as obvious over Furukawa *et al.* (1999). The Office Action asserts that Furukawa *et al.* teach a method of producing an increased yield of an enzyme by cultured CHO cells at 32 °C and that the production of another protein, FVIII, was increased at a temperature of 27 °C. In addition, it is asserted that Furukawa *et al.* teach the use of serum-free media and that under KSR, it is now apparent that "obvious to try" may be an appropriate test in more situations than was previously contemplated, particularly where there are a finite number of identified, predictable solutions. Applicants respectfully assert that the claimed invention is not obvious over the cited reference and traverse the rejection of record.

As stated in *KSR Int'l Co. v. Teleflex Inc.* (127 S. Ct. 1727, 1741 (2007)):

> When there is motivation to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103.

Applicants note that the Office Action argues, in addressing arguments provided in a previously submitted response, that "it would have been obvious to have used any protein in the invention of Furukawa since it is desirable to increase protein yield for experimental or therapeutic use" (Office Action at page 5, paragraph 5) and "that there are only a finite number of predictable potential solutions (the use of CHO cells, for one) to using temperatures in the range of about 27-32°C. Not only is the temperature range small, but protein levels would only be expected to increase, decrease or remain the same" (Office Action at page 5, penultimate paragraph).

At the outset, Applicants respectfully submit that the rejection of record is premised upon a motivation to increase TBP-I protein yield via the culture of CHO cells expressing TBP-1 at reduced temperatures. Thus, the expected or predictable result should be an increase in protein yield and the finite potential solutions to this end is the culturing of CHO cells containing TBP-I encoding nucleic acids at reduced temperatures (in the range of about 27-32°C). A change, or no change, in protein production levels cannot be asserted as one of the finite predictable potential solutions as the Office Action states that "it would have been obvious to have used any protein in the invention of Furukawa since it is desirable to increase protein yield for experimental or therapeutic use" (*i.e.*, the Office Action asserts that this would be the expected outcome of substituting TBP-I encoding nucleic acids into CHO cells taught in Furukawa *et al.*).

In this regard, Applicants respectfully submit that it is not predictable that an increase in protein yield is a predictable result arising from the simple substitution of TBP-I encoding nucleic acids into CHO cells, such as those taught by Furukawa *et al.* As taught in Yoon *et al.*, *Biotechnol.*, 2006, Vol. 122, pp. 463-472 (abstract attached), specific EPO productivity and FSH productivity were decreased by 49% and 22%, respectively, when CHO cells were adapted to growth at temperatures below 37°C. The last sentence of the abstract states: "Improvement of hypothermic cell growth by adaptation does not appear to be applicable for enhanced recombinant protein production, since specific productivity decreases during adaptation to low culture temperature." Thus, it is clear that higher protein yields arising from CHO cells cultured at lower temperatures is unpredictable (increasing in some instances (Furukawa *et al.*) and decreasing in other instances (Yoon *et al.*)). Thus, Applicants respectfully submit that the observed increase in TBP-I production produced by the claimed invention (see Figure 9 and Example 3, pages 16-17) is not a "predictable outcome" arising from a finite number of potential solutions (lowering culture temperatures for CHO cells containing TBP-I encoding nucleic acids). Thus, it is respectfully submitted that the claimed invention is not obvious over the cited reference and reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) is respectfully requested.

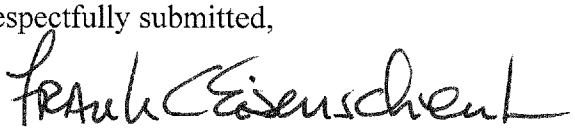
It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of Applicants' agreement with or acquiescence in the Examiner's position. Applicants expressly reserve the right to pursue the invention(s) disclosed in the subject application, including any subject matter canceled or not pursued during prosecution of the subject application, in a related application.

In view of the foregoing remarks and amendments to the claims, Applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,



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Attachment: Yoon *et al.*, abstract only

Select **16253368**

1: J Biotechnol. 2006 Apr 20;122(4):463-72. Epub 2005 Oct 25.

Adaptation of Chinese hamster ovary cells to low culture temperature: cell growth and recombinant protein production.

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Recombinant Chinese hamster ovary (rCHO) cells producing erythropoietin (EPO) and rCHO cells producing follicle-stimulating hormone (FSH) showed a significant increase in specific productivity (q) when grown at 32 degrees C compared to 37 degrees C. However, low culture temperature suppressed cell growth, and therefore, did not increase volumetric productivity as much as q. In an attempt to increase the volumetric productivity through improvement of hypothermic growth, EPO producing rCHO (CHO-EPO) cells and FSH producing rCHO (CHO-FSH) cells were adapted at 32 degrees C in a repeated batch mode using spinner flasks. Cell growth of both CHO-EPO and CHO-FSH gradually improved during adaptation at 32 degrees C. Specific growth rates of CHO-EPO and CHO-FSH cells at 32 degrees C, through adaptation, were increased by 73% and 20%, respectively. During adaptation at 32 degrees C, mRNA levels of cold-inducible RNA-binding protein (CIRP) of both rCHO cell lines did not change significantly, suggesting that CIRP expression may not be the only cause for growth suppression at low culture temperature. Unlike cell growth, the recombinant protein production of both rCHO cell lines was not increased during adaptation due to decreased specific productivities. The specific EPO productivity and specific FSH productivity were decreased by 49% and 22%, respectively. Southern blot analyses showed that the decreased specific productivities were not due to the loss of foreign gene copies. Taken together, improvement of hypothermic cell growth by adaptation does not appear to be applicable for enhanced recombinant protein production, since specific productivity decreases during adaptation to the low culture temperature.

PMID: 16253368 [PubMed - indexed for MEDLINE]

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Effect of low culture temperature on specific productivity and transcription level of anti-4-1BB antibody in recombinant Chinese hamster ovary cells. [Biotechnol Prog. 2003]

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